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Treatment of haemophagocytic lymphohistiocytosis with cyclophosphamide, vincristine and prednisone

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Summary

The goal of this study was to observe the therapeutic efficacy of cyclophosphamide, vincristine and prednisone combined chemotherapy (COP) in treating adult haemophagocytic lymphohistiocytosis (HLH). Fifteen cases diagnosed with HLH were enrolled in our study. Each of them was treated with the COP regimen. Two of the fifteen patients had autoimmune disease-associated HLH (13.3%), 2/15 had lymphoma-associated HLH (13.3%), 7/15 had infection-associated HLH (IAHLH) (46.7%), and the remaining 4/15 developed the disease in the absence of apparent underlying disease (26.7%). A complete response (CR) was achieved in 7/15 patients (46.7%), while a partial response (PR) was achieved in 5/15 patients (33.3%). With a mean follow-up of 72.5 weeks, the one-year overall survival was 66.7%. HLH of varying aetiology exhibited differing sensitivity and response to the COP regimen. In combination with aetiological and supportive treatment, the COP regimen as a mild and cost-effective chemotherapy is especially favourable for IAHLH, autoimmune disease-associated HLH, and disease severity precluding intensive treatment.

Key words: *haemophagocytic lymphohistiocytosis; secondary aetiology; COP regimen*

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a potentially fatal hyperinflammatory syndrome causing persistent high fever, hepatosplenomegaly, pancytopenia and haemophagocytosis in the bone marrow. Features of cytokine flooding, such as IL-6, IL-12, INF-γ and TNF-α, and also high plasma concentrations of sCD25 and sCD163, correlate with the clinical and laboratory manifestations [1–5]. The annual incidence of HLH is estimated at approximately one case per 800,000 individuals [6]. Broadly, HLH can be classified into either familial or secondary HLH. Familial HLH (FHL) is an autosomal recessive disorder with a median survival of less than two months after diagnosis if untreated, with onset typically during infancy or early childhood [1]. Secondary HLH (sHLH) may occur in association with severe infections, malignancies or autoimmune diseases. Although it may subside spontaneously, it may also be associated with pronounced mortality.

Much effort has been expended on controlling the hyperinflammatory syndrome. Aggressive treatments, such as the HLH-2004 protocol and allogeneic haematopoietic stem-cell transplantation (allo-HSCT) [7, 8], are most strongly recommended. However, they have been designed mainly for primary, inherited FHL, normally in patients aged <18 years, as well as any severe form of HLH. Reports on the treatment of sHLH are diverse, and no standard treatment protocol has been established. Currently, the conservative/mild treatments without etoposide, such as corticosteroid/cyclosporine (CsA), intravenous immunoglobulins (IVIG) and the CHOP regimen, have shown varying effectiveness. The cyclophosphamide, vincristine, and prednisone (COP) regimen is used in many haematological diseases [9, 10]. We investigated treatment outcome after its use as another mild immunomodulatory therapy in sHLH patients.

Methods

Patients and diagnosis

From June 2007 to May 2011, 15 patients diagnosed with HLH were enrolled and treated with the COP regimen as either initial or second-line therapy. HLH was diagnosed according to the revised diagnostic guidelines of the Histiocyte Society's HLH Study Group [1]. To rule out a possible underlying disease, e.g. virus or bacterial infection, autoimmune disease and neoplasms (especially lymphoma), we selectively and systematically performed a series of laboratory tests, including culturing of blood, bone marrow or

sputum; screening of tumour markers and autoantibodies; computed tomography (CT) scans; positron emission tomography (PET)/CT; and in some cases lymph-node biopsy. Finally, 11 of 15 patients were identified as having sHLH. Among them, 7 patients were identified as having infection-associated HLH, 2 patients as having autoimmune disease-associated HLH, and another 2 patients as having malignant lymphoma associated with HLH. No underlying disease was found in the remaining 4 patients.

Treatment regimen

Initiation therapy

After diagnosing HLH and investigating any possible underlying disease, we adopted the COP regimen as an initial treatment. The initial therapy included cyclophosphamide (CTX) 0.3 g/m^2 i.v. and vincristine (VCR) 1.4 mg/m^2 i.v., once weekly for the first eight weeks, and prednisone (PRED) 60 mg/m^2/d p.o., for the first 2 weeks, reduced by 50% of the previous dose every 2 weeks until the end of the 7th week, then progressively tapered for 1 week (fig. 1A). CTX and VCR were delayed, provided that the absolute neutrophil count (ANC) was below 0.5×109/L or in the presence of severe myelosuppression. If no improvement of symptoms or laboratory tests was seen on the 14th day of the COP regimen, the patient was switched to an alternative regimen.

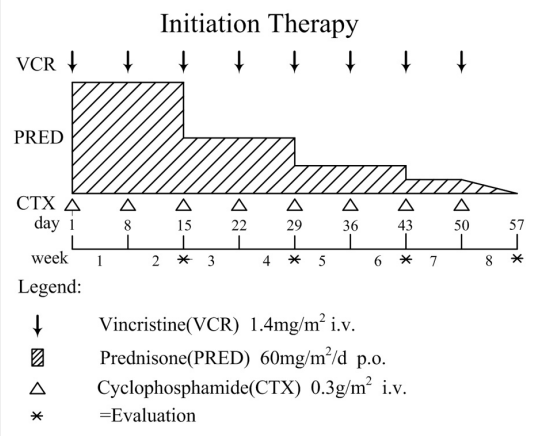

Figure 1A

Overview of initial treatment protocol for secondary hemophagocytic lymphohistiocytosis (sHLH).

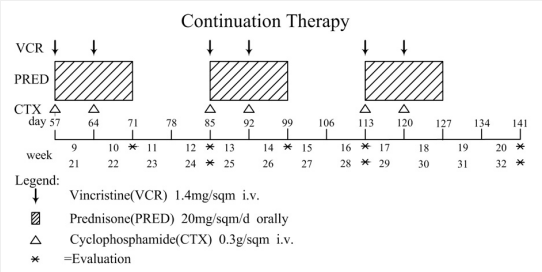

Figure 1B

Overview of continuation treatment protocol for secondary hemophagocytic lymphohistiocytosis (sHLH).

Continuation therapy

Continuation therapy was administered to patients who responded but did not achieve a complete response (CR) after the initial therapy. Once CR was achieved during continuation therapy the treatment of HLH patients with the COP regimen was stopped. Patients were treated with COP (CTX 0.3 g/m^2 i.v. on day 1, day 8; VCR 1.4 mg/m^2 i.v. on day 1, day 8; PRED 20 mg/m^2 p.o., for 14 days). Continuation therapy was repeated every 4 weeks for a total of 4 to 6 cycles in responding patients (fig. 1B). The COP regimen was delayed if ANC was less than 0.5×109/L or in the case of severe myelosuppression. If relapse or refractory disease was identified during continuation therapy, the patient was switched to alternative regimens such as the HLH-2004 treatment protocol, IVIG and other clinical trials.

Subsequent therapy

The aim of subsequent therapy was to sustain remission in patients who had achieved CR. If there were some abnormalities in certain parameters but the patient had not met the definition of relapse [3], the following treatment strategies might be considered: 1. continue the continuation therapy; 2. prolong the intervals between every cycle of treatment described in the continuation therapy protocol; or 3. administer prednisone only in the minimum effective dose.

Supportive therapy

Appropriate broad-spectrum antibiotics were necessary (as determined by culture results), and maximal initial supportive care was suggested. The supportive therapy included prophylactic cotrimoxazole, antimycotic and/or antiviral therapy in suspected patients, and IVIG (during initial and continuation therapy). Supportive transfusion, including red blood cells, platelets, fresh-frozen plasma or cryoprecipitate, was adopted depending on blood cell count, the results of the blood coagulation test and the patient's clinical status.

Evaluation of disease status

Complete response (CR) was defined as disappearance of clinical symptoms and resolution of all signs and laboratory abnormalities. Partial response (PR) was defined as significant but incomplete improvement of clinical and/or biological manifestations. If either of these was aggravated, the response was considered no response (NR). Response was evaluated every two weeks during treatment and at the point of discharge or death. Follow-up, mainly focusing on clinical observation and laboratory detection, was conducted every two weeks for two months and then every month for four months.

Statical analysis

A retrospective analysis of the efficacy of COP chemotherapy was performed. Survival time was calculated from the initial treatment to the time of analysis or death. Statistical significance was determined at a level of $p < 0.05$. The Wilcoxon test was used to calculate the difference in parameters before and after chemotherapy. The software pack-

age SPSS for Windows (version 16.0, SPSS, Chicago, IL, USA) was used for the statistical analysis.

Results

Patient characteristics and laboratory data

The study group consisted of fifteen patients (10 females, 5 males) with ages ranging from 14 to 73 years (median 41 years). Two patients had autoimmune diseases. Two patients were classified as having lymphoma-associated HLH (LAHLH), and seven as having infection-associated HLH (IAHLH). Four patients developed the disease in the absence of apparent underlying disease. Table 1 shows the major clinical and laboratory characteristics of 15 patients with HLH at diagnosis. Most of the patients with HLH presented with high fever (100%), splenomegaly (73.3%), lymphadenectasis (46.7%) and bleeding (46.7%). Hepatomegaly, oedema and rash accounted for 33.3%, while neurological symptoms, jaundice and multi-cavity effusions were each observed in three cases (20.0%).

Bone marrow aspirations were analysed at least once for each patient. Most of them revealed varying degrees of histiocyte proliferation with active haemophagocytosis at the time of diagnosis, except for one patient for whom this condition was detected in her secondary aspiration. Nine of the ten patient samples examined by flow cytometry showed inversion of the $CD4^+/CD8^+$ ratio and a decrease in the number of natural killer (NK) cells; only one patient showed normal expression.

Treatment outcome

A median of 4.0 cycles of chemotherapy (CTX plus VCR) were administered to the patients initially, with a range of 1 to 8 times depending on their different aetiological factors and the conditions of the disease. Six out of the fifteen patients (two with autoimmune disease, three with infections, one of doubtful cause) received 6 to 8 cycles. Eight patients (two with non-Hodgkin's lymphoma [NHL], four with infections and two of unknown aetiology) were given 1 to 4 cycles. Twelve patients did not need continuation therapy, except for three who reached CR at 4 to 6 cycles of continuation therapy. The overall response (OR) rate was 80.0%, consisting of seven CR and five PR. Three patients showed NR to this therapy. All the CR cases are currently alive, having had either long-term treatment or short-term treatment with a mild infection.

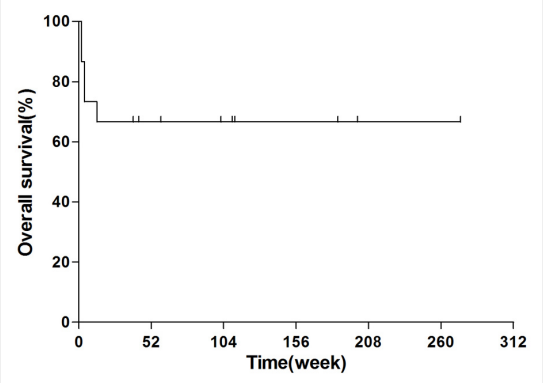

Figure 2

The one-year probability of overall survival of the fifteen patients with sHLH treated with COP regimen was 66.7%.

We performed a mean follow-up duration of 72.5 weeks (range 2–204 weeks) for each patient until the cut-off time of May 13, 2011. The one-year probability of overall survival (OS) was 10/15 (66.7%) (fig. 2). One patient (case 3) with NHL and another (case 11) with EBV infection showed no response to chemotherapy and died within two weeks. One (case 7, 69 yrs) with MRSA infection obtained PR after 4 episodes of chemotherapy (CTX plus VCR) but had only four weeks' duration and died after rapid reduction of the prednisone dose. Another (case 9) with CMV infection also succumbed to early reduction of the steroid dose and the resulting severe pneumonia. The last patient who died (case 13) without obvious underlying aetiology showed aggravated disease after one episode of initial chemotherapy. The HLH-2004 treatment protocol was used as a salvage strategy, but the patient still died of severe myelosuppression. The detailed data are shown in tables 2 and 3.

The levels of most laboratory parameters such as neutrophil counts, platelet counts (PLT), serum ferritin (SF), lactate dehydrogenase (LDH) and fibrinogen (FIB) improved significantly after chemotherapy when compared with levels at disease onset (means ± standard deviations, $P < 0.05$, data not shown). However, no significant change in HGB and TG was identified.

Toxicities

All 15 patients were assessed for toxicities associated with the COP regimen. Table IV summarises grade I–III haematological and non-haematological toxicities of the COP regimen administered to 15 patients. Toxicities were predominantly grade I or II, which most patients could tolerate well without requiring dose reduction of the full-dose COP, such that 86.7% of the intended dose was delivered throughout the chemotherapy regimen. One older patient (6.67%) suffered grade-III myelosuppression, and another (6.67%) experienced grade-III pneumonia. The most common non-haematological toxicity was gastrointestinal toxicity, e.g., nausea/vomiting, stomatitis and transient constipation. However, these patients were all well controlled with supportive management and were able to complete the chemotherapy safely. No renal or cardiac toxicity was observed. No patient developed a secondary tumour.

Discussion

Though we enrolled these patients according to the diagnostic criteria of the HLH-2004 protocol, all were consistent with the new diagnostic criteria proposed by the American Society of Hematology (ASH), 2009 [11]. Hepatitis was added to the criteria for the first time, while hypertriglyceridaemia and hypofibrinogenaemia were downgraded as auxiliary rather than primary results. In our study, 80.0% of patients displayed ALT/AST increases, while 66.7% presented hypofibrinogenaemia, and only 60.0% hypertriglyceridaemia, apparently offering more evidence in support of the new criteria. The hepatitis was mild and sensitive to our treatment: a significant reduction of ALT

levels was found after chemotherapy (P = 0.019). In terms of reflecting the efficacy of the COP regimen, the SF, neutrophilic granulocyte, PLT and serum LDH levels were confirmed by assessment values. However, we did not observe any significant change in the TG level, which has been suggested as a surrogate marker for diagnosis of HLH and evaluation of treatment response [12].

In our study we witnessed an encouraging outcome after treating patients with the COP regimen. The overall response rate was 80% (CR 46.7% + PR 33.3%), and the one-year probability of OS was 66.7%. A large series of children treated with HLH-94 showed a 75% complete remission rate and 3-year OS of 55% ± 9% [13]. Another survey observed 73% CR and 24% PR with a combination of antithymocyte globulins (ATG) with corticosteroids, cyc-

Table 1: Clinical and laboratory characteristics of 15 patients with HLH at diagnosis.

Characteristics	No. (%) of patients	Characteristics	No. (%) of patients
Age, years	44, range 14–73	Jaundice	3 (20.0)
Gender		Laboratory finding	
Male/female	5 (33.3)/10 (66.7)	PLT (<100×10^9/L)	15 (100)
Underlying cause		Neu (<1.0×10^9/L)	10 (66.7)
Infection	7 (46.7)	Hb (<90 g/L)	8 (53.3)
Autoimmune disease	2 (13.3)	SF (≥500 g/L)	15 (100)
Malignant lymphoma	2 (13.3)	FIB (<1.5 g/L)	10 (66.7)
Unknown cause	4 (26.7)	TG (>3 mmol/L)	9 (60.0)
Clinical manifestation		Increased ALT/AST	12 (80.0)
Persistent fever	15 (100)	Increased LDH	14 (93.3)
Splenomegaly	11 (73.3)	Increased TIBL	5 (33.3)
Lymphadenectasis	7 (46.7)	Increased VLDL/Decreased HDL	10 (66.7)
Bleeding	7 (46.7)	Prolonged PT/APTT	8 (53.3)
Hepatomegaly	5 (33.3)	Hyponatremia	8 (53.3)
Oedema	5 (33.3)	Hypoproteinemia	11 (73.3)
Rash	5 (33.3)	BM hemophagocytosis	14 (93.3)
Multicavity effusion	3 (20.0)		
Neurological symptom	3 (20.0)		

PLT, platelets; Neu, neutrophil; Hb, haemoglobin; SF, serum ferritin; FIB, fibrinogen; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TBIL, total bilirubin; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; PT, prothrombin time; APTT, activated partial thromboplastin time; BM, bone marrow.

Table 2: Detailed treatment course and prognosis.

NO.	Gender/Age	Aetiology	Chemotherapy (VCR+CTX) times of initial therapy	Continuation therapy cycle	Treatment effect	Survival time (W)	Salvage	Prognosis
1	Female/14	Autoimmune disease	6	0	CR	204	no	Alive
2	Female/38	Autoimmune disease	8	12	CR	59	no	Alive
3	Female/41	Malignant lymphoma	2	0	NR	2	no	Death
4	Male/42	Malignant lymphoma	3	0	PR	186	allo-HSCT	Alive
5	Female/19	Infection (MRSA)	2	0	CR	110	no	Alive
6	Female/27	Infection (CMV)	8	8	CR	112	no	Alive
7	Female/69	Infection (MRSA)	4	0	PR	4	no	Death
8	Male/32	Infection (bacteria)	2	0	CR	164	no	Alive
9	Female/25	Infection (CMV)	7	0	PR	13	no	Death
10	Female/63	Infection (bacteria)	8	8	CR	39	no	Alive
11	Female/56	Infection (EBV)	1	0	NR	2	HLH-2004	Death
12	Male/69	Unknown cause	6	0	CR	102	no	Alive
13	Female/53	Unknown cause	1	0	NR	4	HLH-2004	Death
14	Male/40	Unknown cause	2	0	PR	43	no	Alive
15	Male/73	Unknown cause	5	0	PR	43	no	Alive

MRSA, methicillin resistant staphylococcus aureus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; allo-HSCT, allogene haematopoietic stem-cell transplantation.

Table 3: Response rate of HLH depending on aetiology.

Aetiology	Response rate			
	Total	CR	PR	NR
Total	15	7 (46.7%)	5 (33.3%)	3 (20.0%)
Autoimmune disease	2	2 (100.0%)	0 (0.0%)	0 (0.0%)
Malignant lymphoma	2	0 (0.0%)	1 (50.0%)	1 (50.0%)
Infection	7	4 (57.1%)	2 (28.6%)	1 (14.3%)
Unknown cause	4	1 (25.0%)	2 (50.0%)	1 (25.0%)

CR, complete response; PR, partial response; NR, no response.

losporine A and intrathecal injections of methotrexate [14]. When referring to adults, Shin reported an OR of 58.8% (CR 41.2% + PR 17.6%) and 43.9% two-year OS with the CHOP regimen [15]. Despite differences in the combination of patient series and age distributions, our results are in accordance with these previous studies. Interestingly, patients with different aetiologies showed different responses to the COP regimen. IAHLH is most sensitive to it, especially bacteria-induced cases. A short course is often enough in younger patients. When a relatively longer treatment course was needed in older patients and in virus-associated HLH (VAHLH) other than EBV, IVIG supplementation was helpful. EBV-HLH is associated with high mortality. Patients with EBV infection in our study progressed rapidly and died quickly, a course which could not be controlled through use of the COP regimen. Early institution of etoposide-containing treatment may improve survival [16]. As many as half of the patients with HLH secondary to autoimmune disease may respond to corticosteroids alone [17, 18]. Aggressive supportive management and high-dose corticosteroids were recommended as an initial step by some authors, while CsA, etoposide, IVIG, plasma exchange and allo-HSCT have been suggested as second-line therapies for refractory disease [17, 19]. In our series use of the COP regimen yielded a satisfactory prognosis for the patients with autoimmune disease-associated HLH. Conceivably it suppressed the disturbed immune system, which is the common pathological mechanism of both autoimmune disease and HLH. After use of the COP regimen to reduce disease severity, HLH gradually subsided in some patients with unknown aetiologies. Malignancy-associated HLH (MAHLH) often impedes adequate treatment of malignancy and has the worst outcome compared with any other form of HLH. In our study we adopted the COP regimen to control the existing HLH before malignant lymphoma was certified. One patient showed no response and died rapidly. Another, although PR was achieved, might still have had a poor prognosis if no allo-HSCT had been administered. In our opinion the COP regimen may not be sufficient when treating patients with MAHLH. First-line chemotherapy is of the utmost importance, and allo-HSCT should be considered in eligible individuals, as reported by Balwierz [20]. The COP protocol did relieve the symptoms and laboratory abnormalities of HLH triggered by an activated immune system. However, treatment aimed directly at the aetiology may cure the disease more efficiently. It is therefore important to find the underlying disease causing sHLH. If the COP regimen is administered too early it may conceal aetiological factors and be unfavourable for prognosis, even if the HLH is definite. Combining the COP regimen with aetiological treatment and aggressive supportive therapy seems to work best.

Currently, national multicentre research on the efficacy of the HLH-2004 treatment protocol is underway; however, related reports are rare at present. Zhu reported that 7/14 paediatric patients (50%) who were treated with the HLH-2004 protocol ultimately died; 4/14 relapsed or showed unremitting activation [21]. Patrick observed that 5/17 paediatric patients (29.4%) experienced severe neurological toxicity while being treated with the HLH-2004 treatment protocol [22]. Cardiotoxicity has been reported as a side effect of etoposide, primarily in adults [23]. Seo even reported a case of therapy-related acute monocytic leukaemia following low-dose etoposide treatment for HLH [24]. In our series we treated a 53-year-old patient with relapsed disease using the HLH-2004 treatment protocol as a salvage strategy. Unfortunately the myelosuppression was so severe that she died of an uncontrollable opportunistic infection. In another report of 10 adult cases treated with the recommended HLH-2004 protocol in our department, mortality was as high as 60% [25]. In contrast, common side effects of chemotherapy, such as anorexia, nausea, vomiting, constipation and peripheral neuropathy, were so mild in our study that relief was obtained through appropriate supportive care. Furthermore, myelosuppression was mainly grade I–II without obvious renal or cardiac toxicities. Patients with HLH usually present severe disease status at the time of onset. The COP regimen may be more suitable than other chemotherapy regimens, such as HLH-2004 and CHOP. In HLH patients who presented with bacterial infection or autoimmune disease, or patients who cannot tolerate intensive chemotherapy due to old age or disease severity, the COP regimen may be the first choice for treatment.

In conclusion, COP chemotherapy had a relatively favourable effect for adult patients with sHLH, and the toxicities were tolerable. However, the heterogeneous prognosis depends, to some extent, on different aetiological factors and the choice of treatment. Given the small number of patients included, further studies should enroll more patients.

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Table 4: Toxicities associated with COP chemotherapy.

Toxicity	Grade (WHO)		
	I	II	III
Anaemia	5 (33.3%)	3 (20.0%)	0 (0.0%)
Neutropenia	3 (20.0%)	2 (13.3%)	1 (6.67%)
Thrombocytopenia	3 (20.0%)	1 (6.67%)	1 (6.67%)
Infection	4 (26.7%)	3 (20.0%)	1 (6.67%)
Nausea/vomiting/stomatitis	5 (33.3%)	4 (26.7%)	0 (0.0%)
Constipation	4 (26.7%)	1 (6.67%)	0 (0.0%)
Peripheral neurotoxicity	1 (6.67%)	0 (0.00%)	0 (0.0%)
Alopecia	3 (20.0%)	0 (0.00%)	0 (0.0%)

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Figures (large format)

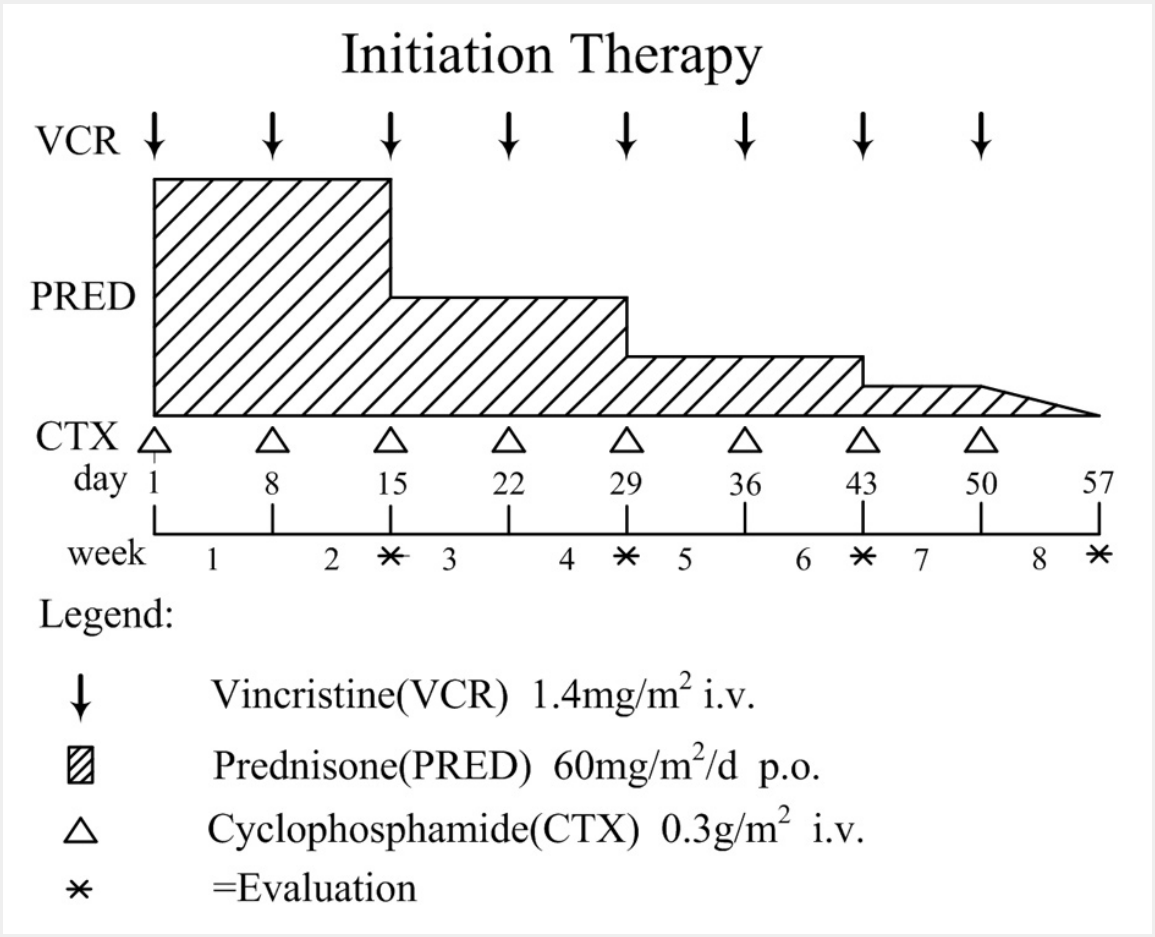

Figure 1A

Overview of initial treatment protocol for secondary hemophagocytic lymphohistiocytosis (sHLH).

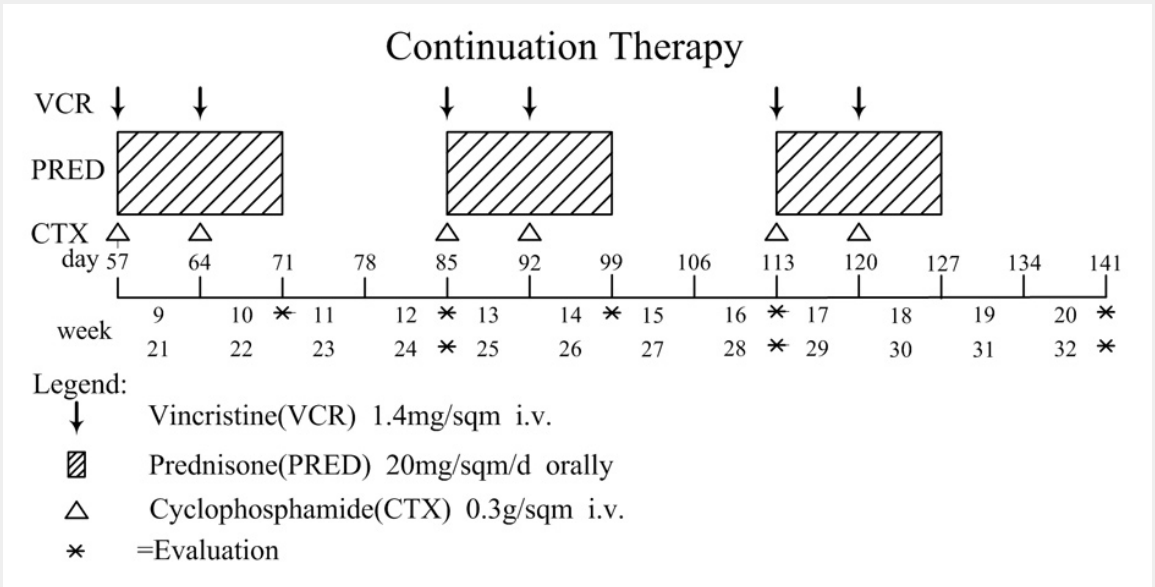

Figure 1B

Overview of continuation treatment protocol for secondary hemophagocytic lymphohistiocytosis (sHLH).

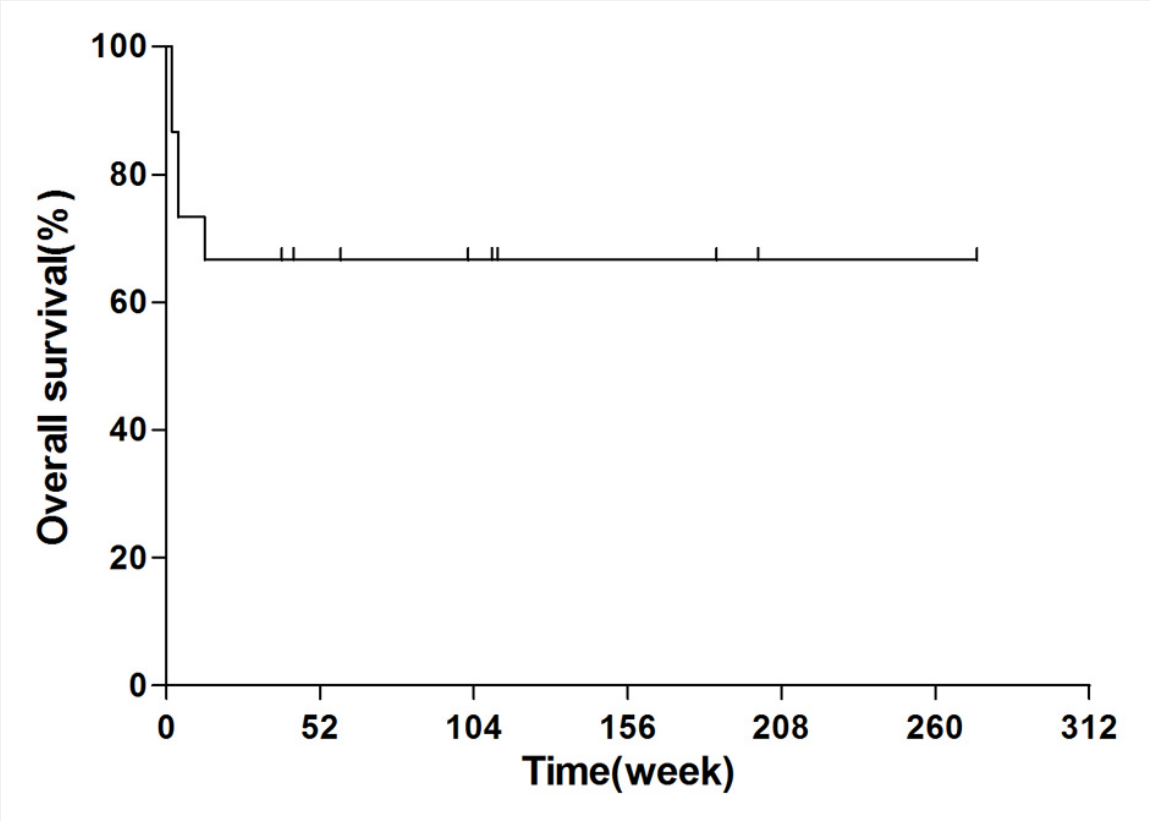

Figure 2

The one-year probability of overall survival of the fifteen patients with sHLH treated with COP regimen was 66.7%.